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C2C
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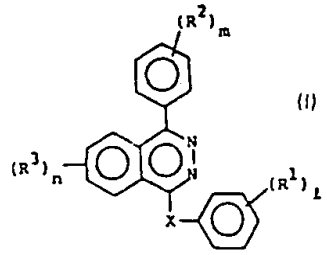
(54) 4-Phenylphthalazine derivatives

(57) 4-phenylphthalazine derivatives of formula (I), and represented by pharmaceutically acceptable salts thereof have potent inhibitory activities against platelet aggregation



(I)

wherein X is NH or O; R^1, R^2 and R^3 are each alkyl, alkoxy, halogen, alkoxycarbonyl, carboxyl, alkylcarbonyl group, hydroxyl, trifluoromethyl, and R^1 can also be cyano, l, m and n are each 0, 1, 2 or 3 (provided that l = 1 to 3 and m = n = zero when X is O, and the case where l = m = n = zero is excluded when X is NH).

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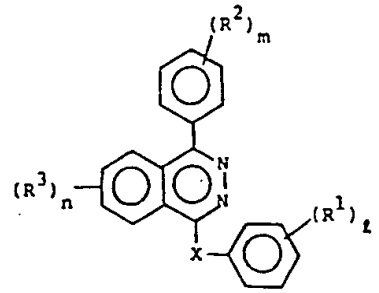
SPECIFICATION

4-phenylphthalazine derivatives

This invention relates to a 4-phenylphthalazine derivative represented by the following formula [I] or a pharmaceutically acceptable salt thereof:



[I]

wherein X stands for NH or O; R^1 an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a halogen atom, an alkoxycarbonyl group having 2 to 6 total carbon atoms, a carboxyl group, a cyano group, an alkylcarbonyl group having 2 to 4 total carbon atoms, a hydroxyl group or a trifluoromethyl group; R^2 and R^3, which may be identical or different (may also be the same as or different from R^1), each represent an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a halogen atom, an alkoxycarbonyl group having 2 to 6 total carbon atoms, a carboxyl group, an alkylcarbonyl group having 2 to 4 total carbon atoms, a hydroxyl group or a trifluoromethyl group; and each of l, m and n is an integer of zero to 3 (provided that l=1 to 3 and m=n=zero when X is O, and the case where l=m=n=zero is excluded when X is NH), each plural number of R^1, R^2 and R^3 being identical or different when the integers l, m and n are two or more,

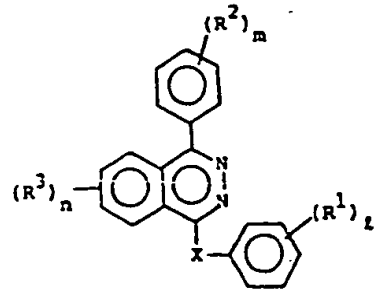
and also to a process for producing the same.

As 4-phenylphthalazine derivatives analogous to those of the present invention, there have heretofore been known 1-anilino-4-phenylphthalazine (Ber., *38*, 3923 (1905)], 1-phenoxy-4-phenylphthalazine [Journal of Pharmacology, *88*, 83 (1968)], 1-[2-(2-methylallyl)-phenoxy]-4-phenylphthalazine, 1-(2-allylphenoxy)-4-phenylphthalazine [Chem. Pharm. Bull., *24*, 1581—1595 (1976)]. These compounds are disclosed merely as intermediates and there is nothing done about uses thereof. The compounds 1-[2-(2-methylallyl)phenoxy]-4-phenylphthalazine and 1-(2-allylphenoxy)-4-phenylphthalazine are liable to undergo ring-closure reaction or other undesirable reactions due to the presence of double bonds in the substituents, whereby structural changes are caused.

On the other hand, studies have been made about 1-alkylamino-4-phenylphthalazine derivatives, 1-alkoxy-4-phenylphthalazine derivative [J. Med.Chem. *12*, 555 (1969)] and 1-(piperazine-1-yl)-4-phenylphthalazine derivative (Japanese Patent Publication 39944/1973) for their uses as antiinflammatory agents. However, there is no description about 1-anilino derivatives and 1-phenoxy derivatives.

The present inventors have successfully synthesized the novel compounds represented by the above formula [I] which have not been described in literatures. They have further progressed their studies to find out that these compunds have potent inhibitory activity against platelet aggregation. Thus, the compounds of the present invention are considered to be applicable for prevention or therapy of the diseases induced by increased platelet aggregation ability such as cerebral thrombosis, cerebral infarction, myocardial infarction and arteriosclerotic diseases. It is therefore the primary object of the present invention to provide a novel compound represented by the formula [I] having a potent inhibitory activity against platelet aggregation.

The compound according to the present invention is represented by the following formula [I]:



[I]

wherein all the symbols have the same meanings as defined above.

In the above formula [I], the alkyl group as represented by R^1, R^2 and R^3 may be exemplified by methyl, ethyl, propyl, iso-propyl, n-butyl, t-butyl and amyl. Typical examples of the alkoxy group are methoxy, ethoxy, propoxy, butoxy and amyloxy. As a halogen atom, there may be mentioned fluorine, chlorine, bromine and iodine. The alkoxycarbonyl group may include, for example, methoxycarbonyl, ethoxycarbonyl, propoxycarbonyl, butoxycarbonyl, amyloxycarbonyl, etc. As the alkylcarbonyl group, there may be used acetyl, propionyl, butylyl or others.

In the compounds of the present invention, R^1 may preferably be an alkyl group, an alkoxy group, a halogen atom or a trifluoromethyl group. On the other hand, R^2 may preferably be an alkyl group, an alkoxy group or a halogen atom, while R^3 an alkyl group.

In the above formula [I], each of the integers represented by l, m and n may be variable from zero to 3. But there are some restrictions depending on the species of X. When X represents O (an oxygen atom), both m and n are required to be zero, while l may be variable from 1 to 3. On the other hand, when X represents NH group, the case where all of the integers are zero is excluded; in other words, there is at least one substituent on the aromatic nuclei. Thus, when X is NH, there are so many possible combinations in number of the substituents on the aromatic nuclei. Among them, the following four combinations are found to be particularly preferred:

(1) l=1 to 3, m=n=zero;
(2) l=1 to 2, m=1 to 2, n=zero;
(3) l=1 to 2, m=zero, n=1 to 2; and
(4) l=m=zero, n=1 to 2.

Also, when X is O, l is preferred to be 1 or 2, while m=n=0.

The compound represented by the formula [I] can also form a pharmaceutically acceptable salt through the reaction of the basic nitrogen thereof with an acid. For example, there may be mentioned salts with mineral acids such as hydrogen chloride, sulfuric acid, hydrobrobromic acid, phosphoric acid, etc. or methanesulfonic acid, toluenesulfonic acid, benzenesulfonic acid, acetic acid, glycolic acid, glucuronic acid, maleic acid, oxalic acid, ascorbic acid, citric acid, salicylic acid, and so on.

In the following, there are enumerated concrete examples of the compounds represented by the formula [I].

Compound No.	*Name of Compound*
(1)	1-(4-Methylanilino)-4-phenylphthalazine
(2)	1(3-Methylanilino)-4-phenylphthalazine
(3)	1-(2-Methylanilino)-4-phenylphthalazine
(4)	1-(4-Ethylanilino)-4-phenylphthalazine
(5)	1-(2-Ethylanilino)-4-phenylphthalazine
(6)	1-(4-n-Butylanilino)-4-phenylphthalazine
(7)	1-(3-n-Butylanilino)-4-phenylphthalazine
(8)	1-(4-t-Butylanilino)-4-phenylphthalazine
(9)	1-(4-Methoxyanilino)-4-phenylphthalazine
(10)	1-(3-Methoxyanilino)-4-phenylphthalazine
(11)	1-(3-Propoxyanilino)-4-phenylphthalazine
(12)	1-(4-n-Butoxyanilino)-4-phenylphthalazine
(13)	1-(4-Fluoroanilino)-4-phenylphthalazine
(14)	1-(3-Fluoroanilino)-4-phenylphthalazine
(15)	1-(2-Fluoroanilino)-4-phenylphthalazine
(16)	1-(4-Chloroanilino)-4-phenylphthalazine
(17)	1-(3-Chloroanilino)-4-phenylphthalazine
(18)	1-(2-Chloroanilino)-4-phenylphthalazine
(19)	1-(4-Bromoanilino)-4-phenylphthalazine
(20)	1-(3-Bromoanilino)-4-phenylphthalazine
(21)	1-4-Iodoanilino)-4-phenylphthalazine
(22)	1-(3-Iodoanilino)-4-phenylphthalazine
(23)	1-(4-Ethoxycarbonylanilino)-4-phenylphthalazine
(24)	1-(4-Carboxylanilino)-4-phenylphthalazine
(25)	1-(4-Cyanoanilino)-4-phenylphthalazine
(26)	1-(4-Acetylanilino)-4-phenylphthalazine
(27)	1-(4-Trifluoromethylanilino)-4-phenylphthalazine
(28)	1-(3-Trifluoromethylanilino)-4-phenylphthalazine
(29)	1-(2-Trifluoromethylanilino)-4-phenylphthalazine
(30)	1-(3-Hydroxylanilino)-4-phenylphthalazine

Compound No.	Name of Compound
(31)	1-(2,3-Dimethylanilino)-4-phenylphthalazine
(32)	1-(2,4-Dimethylanilino)-4-phenylphthalazine
(33)	1-(2,5-Dimethylanilino)-4-phenylphthalazine
(34)	1-(3,4-Dimethylanilino)-4-phenylphthalazine
(35)	1-(2,5-Diethylanilino)-4-phenylphthalazine
(36)	1-(2,5-Dipropylanilino)-4-phenylphthalazine
(37)	1-(2,5-Dimethoxyanilino)-4-phenylphthalazine
(38)	1-(3,4-Dimethoxyanilino)-4-phenylphthalazine
(39)	1-(2,5-Dichloroanilino)-4-phenylphthalazine
(40)	1-(3,4-Dichloroanilino)-4-phenylphthalazine
(41)	1-(2,5-Difluoroanilino)-4-phenylphthalazine
(42)	1-(3-Chloro-4-methylanilino)-4-phenylphthalazine
(43)	1-(2-Methyl-3-chloroanilino)-4-phenylphthalazine
(44)	1-(2-Methyl-4-chloroanilino)-4-phenylphthalazine
(45)	1-(3-Methyl-4-chloranilino)-4-phenylphthalazine
(46)	1-(3-Fluoro-4-methylanilino)-4-phenylphthalazine
(47)	1-(2-Methoxy-5-methylanilino)-4-phenylphthalazine
(48)	1-(5-Chloro-2-methoxyanilino)-4-phenylphthalazine
(49)	1-(2-Methyl-5-trifluoromethylanilino)-4-phenylphthalazine
(50)	1-(2-Methoxy-5-trifluoromethylanilino)-4-phenylphthalazine
(51)	1-(2,4,6-Trimethylanilino)-4-phenylphthalazine
(52)	1-(3,4,5-Trimethoxyanilino)-4-phenylphthalazine
(53)	1-Anilino-4-(4-methylphenyl)phthalazine
(54)	1-(4-Methylanilino)-4-(4-methylphenyl)phthalazine
(55)	1-(4-Butylanilino)-4-(4-methylphenyl)phthalazine
(56)	1-(2,5-Dimethylanilino)-4-(4-methylphenyl)phthalazine
(57)	1-(3-Methoxyanilino)-4-(4-methylphenyl)phthalazine
(58)	1-(4-Butoxyanilino)-4-(4-methylphenyl)phthalazine
(59)	1-(2,5-Dimethoxyanilino)-4-(4-methylphenyl)phthalazine
(60)	1-(3-Chloroanilino)-4-(4-methylphenyl)phthalazine
(61)	1-(3-Bromoanilino)-4-(4-methylphenyl)phthalazine
(62)	1-(3-Fluoroanilino)-4-(4-methylphenyl)phthalazine
(63)	4-(4-Methylphenyl)-1-(3-trifluoromethylanilino)phthalazine
(64)	1-(5-Chloro-2-methoxyanilino)-4-(4-methylphenyl)phthalazine
(65)	1-(3-Chloro-4-methylanilino)-4-(4-methylphenyl)phthalazine
(66)	1-(4-Ethoxycarbonylanilino)-4-(4-methylphenyl)phthalazine
(67)	1-Anilino-4-(4-butylphenyl)phthalazine
(68)	4-(4-Butylphenyl)-1-(2,5-dimethylanilino)phthalazine
(69)	4-(4-Butylphenyl)-1-(2,5-dimethoxyanilino)phthalazine
(70)	4-(4-Butylphenyl)-1-(3-chloroanilino)phthalazine
(71)	4-(4-Butylphenyl)-1-(3-trifluoromethylanilino)phthalazine
(72)	4-(4-Butylphenyl)-1-(5-chloro-2-methoxyanilino)phthalazine
(73)	1-Anilino-4-(2,4-dimethylphenyl)phthalazine
(74)	1-Anilino-4-(4-methoxyphenyl)phthalazine
(75)	1-(4-Butylanilino)-4-(4-methoxyphenyl)phthalazine
(76)	1-(2,5-Dimethylanilino)-4-(4-methoxyphenyl)phthalazine
(77)	1-(2,5-Dimethoxyanilino)-4-(4-methoxyphenyl)phthalazine
(78)	1-(3-Chloroanilino)-4-(4-methoxyphenyl)phthalazine
(79)	4-(4-Methoxyphenyl)-1-(3-trifluoromethylanilino)phthalazine
(8)	1-(5-Chloro-2-methoxyanilino)-4-(4-methoxyphenyl)phthalazine
(81)	1-(4-ethoxycarbonylanilino)-4-(4-methoxyphenyl)phthalazine
(82)	1-Anilino-4-(4-butoxyphenyl)phthalazine
(83)	4-(4-Butoxyphenyl)-1-(2,5-dimethylanilino)phthalazine
(84)	4-(4-Butoxyphenyl)-1-(2,5-dimethoxyanilino)phthalazine
(85)	4-(4-Butoxyphenyl)-1-(3-chloroanilino)phthalazine
(86)	4-(4-Butoxyphenyl)-1-(3-trifluoromethylanilino)phthalazine
(87)	4-(4-Butoxyphenyl)-1-(5-chloro-2-methoxyanilino)phthalazine
(88)	1-Anilino-4-(2,4-dimethoxyphenyl)phthalazine
(89)	1-(2,5-Dimethylanilino)-4-(2,4-dimethoxyphenyl)phthalazine
(90)	1-(2,5-Dimethoxyanilino)-4-(2,4-dimethoxyphenyl)phthalazine
(91)	1-(3-Chloroanilino)-4-(2,4-dimethoxyphenyl)phthalazine
(92)	4-(2,4-Dimethoxyphenyl)-1-(3-trifluoromethylanilino)-phthalazine
(93)	1-(5-Chloro-2-methoxyanilino)-4-(2,4-dimethoxyphenyl)-phthalazine

(94) 1-Anilino-4-(4-chlorophenyl)phthalazine
(95) 4-(4-Chlorophenyl)-1-(2,5-dimethylanilino)phthalazine
(96) 4-(4-Chlorophenyl)-1-(2,5-dimethoxyanilino)phthalazine
(97) 1-(3-Chloroanilino)-4-(4-chlorophenyl)-phthalazine
(98) 4-(4-Chlorophenyl)-1-(3-trifluoromethylanilino)phthalazine
(99) 1-(5-Chloro-2-methoxyanilino)-4-(4-chlorophenyl)phthalazine
(100) 1-Anilino-4-(4-bromophenyl)phthalazine
(101) 1-Anilino-4-(4-fluorophenyl)phthalazine
(102) 1-(2,5-Dimethylanilino)-4-(4-fluorophenyl)phthalazine
(103) 1-(2,5-Dimethoxyanilino)-4-(4-fluorophenyl)phthalazine
(104) 1-(3-Chloroanilino)-4-(4-fluorophenyl)phthalazine
(105) 4-(4-Fluorophenyl)-1-(3-trifluoromethylanilino)phthalazine
(106) 1-(5-Chloro-2-methoxyanilino)-4-(4-fluorophenyl)phthalazine
(107) 1-Anilino-4-(4-ethoxycarbonylphenyl)phthalazine
(108) 1-(2,5-Dimethylanilino)-4-(4-ethoxycarbonylphenyl)phthalazine
(109) 1-(2,5-Dimethoxyanilino)-4-(4-ethoxycarbonylphenyl)phthalazine
(110) 1-(3-Chloroanilino)-4-(4-ethoxycarbonylphenyl)phthalazine
(111) 4-(4-Ethoxycarbonylphenyl)-1-(3-trifluoromethylanilino)phthalazine
(112) 1-(5-Chloro-2-methoxyanilino)-4-(4-ethoxycarbonylphenyl)phthalazine
(113) 1-Anilino-6-methyl-4-phenylphthalazine
(114) 1-Anilino-7-methyl-4-phenylphthalazine
(115) 1-(2,5-Dimethylanilino)-6-methyl-4-phenylphthalazine
(116) 1-(2,5-Dimethylanilino)-7-methyl-4-phenylphthalazine
(117) 1-(2,5-Dimethylanilino)-6-methyl-4-phenylphthalazine
(118) 1-(2,5-Dimethoxyanilino)-7-methyl-4-phenylphthalazine
(119) 1-(3-Chloroanilino)-6-methyl-4-phenylphthalazine
(120) 1-(3-Chloroanilino)-7-methyl-4-phenylphthalazine
(121) 6-Methyl-4-phenyl-1-(3-trifluoromethylanilino)phthalazine
(122) 7-Methyl-4-phenyl-1-(3-trifluoromethylanilino)phthalazine
(123) 1-(5-Chloro-2-methoxyanilino)-6-methyl-4-phenylphthalazine
(124) 1-(5-Chloro-2-methoxyanilino)-7-methyl-4-phenylphthalazine
(125) 1-Anilino-6,7-dimethyl-4-phenylphthalazine
(126) 1-(4-Butylanilino)-6,7-dimethyl-4-phenylphthalazine
(127) 1-(2,5-Dimethylanilino)-6,7-dimethyl-4-phenylphthalazine
(128) 1-(2,5-Dimethoxyanilino)-6,7-dimethyl-4-phenylphthalazine
(129) 1-(4-Butoxyanilino)-6,7-dimethyl-4-phenylphthalazine
(130) 1-(3-Chloroanilino)-6,7-dimethyl-4-phenylphthalazine
(131) 6,7-Dimethyl-4-phenyl-1-(3-trifluoromethylanilino)phthalazine
(132) 1-(5-Chloro-2-methoxyanilino)-6,7-dimethyl-4-phenylphthalazine
(133) 1-(3-Chloro-4-methylanilino)-6,7-dimethyl-4-phenylphthalazine
(134) 6,7-Dimethyl-1-(4-ethoxycarbonylanilino)-4-phenylphthalazine
(135) 1-Anilino-5,8-dimethyl-4-phenylphthalazine
(136) 1-(3-Chloroanilino)-5,8-dimethyl-4-phenylphthalazine
(137) 1-Anilino-6,7-dibutyl-4-phenylphthalazine
(138) 1-Anilino-6,7-dimethoxy-4-phenylphthalazine
(139) 6,7-Dimethoxy-1-(2,5-dimethylanilino)-4-phenylphthalazine
(140) 6,7-Dimethoxy-1-(2,5-dimethoxyanilino)-4-phenylphthalazine
(141) 1-(3-Chloroanilino)-6,7-dimethoxy-4-phenylphthalazine
(142) 6,7-Dimethoxy-4-phenyl-1-(3-trifluoromethylanilino)phthalazine
(143) 1-(5-Chloro-2-methoxyanilino)-6,7-dimethoxy-4-phenylphthalazine
(144) 1-(4-Butylanilino)-6,7-dimethoxy-4-phenylphthalazine
(145) 1-(4-Butoxyanilino)-6,7-dimethoxy-4-phenylphthalazine
(146) 1-Anilino-5,8-dimethoxy-4-phenylphthalazine
(147) 1-Anilino-6,7-dibutoxy-4-phenylphthalazine
(148) 1-Anilino-6,7-dichloro-4-phenylphthalazine
(149) 6,7-Dichloro-1-(2,5-dimethylanilino)-4-phenylphthalazine
(150) 6,7-Dichloro-1-(2,5-dimethoxyanilino)-4-phenylphthalazine
(151) 1-(3-Chloroanilino)-6,7-dichloro-4-phenylphthalazine
(152) 6,7-Dichloro-4-phenyl-1-(3-trifluoromethylanilino)phthalazine
(153) 1-(4-Chloro-2-methoxyanilino)-6,7-dichloro-4-phenylphthalazine
(154) 1-Anilino-5,8-dichloro-4-phenylphthalazine
(155) 1-Anilino-6-ethoxycarbonyl-4-phenylphthalazine
(156) 1-Anilino-6,7-dimethyl-4-(4-methylphenyl)phthalazine
(157) 1-(4-Butylanilino)-6,7-dimethyl-4-(4-methylphenyl)phthalazine
(158) 6,7-Dimethyl-1-(2,5-dimethylanilino)-4-(4-methylphenyl)phthalazine

(159) 6,7-Dimethyl-1-(3-methoxyanilino)-4-(4-methylphenyl)phtha azine
(160) 1-(2,5-Dimethoxyanilino)-6,7-dimethyl-4-(4-methylphenyl)-p thalazine
(161) 1-(3-Chloroanilino)-6,7-dimethyl-4-(4-methylphenyl)phtha'a ne
(162) 6,7-Dimethyl-4-(methylphenyl)-1-(3-trifluoromethylanilino ph thalazine
(163) 1-(4-Chloro-2-methoxyanilino)-6,7-dimethyl-4-(4-methylphenyl)phthalazine
(164) 6,7-Dimethyl-1-(4-ethoxycarbonylanilino)-4-(4-methylphenyl)phthalazine
(165) 1-Anilino-4-(4-butylphenyl)-6,7-dimethylphthalazine
(166) 1-Anilino-6,7-dimethyl-4-(4-methoxyphenyl)phthalazine
(167) 6,7-Dimethyl-1-(2,5-dimethylanilino)-4-(4-methoxyphenyl)phthalazine
(168) 1-(2,5-Dimethoxyanilino)-6,7-dimethyl-4-(4-methoxyphenyl)phthalazine
(169) 1-(3-Chloroanilino)-6,7-dimethyl-4-(4-methoxyphenyl)phthalazine
(170) 6,7-Dimethyl-4-(4-methoxyphenyl)-1-(3-trifluoromethylanilino)phthalazine
(171) 1-(5-Chloro-2-methoxyanilino)-6,7-dimethyl-4-(4-methoxyphenyl)phthalazine
(172) 1-Anilino-4-(4-butoxyphenyl)-6,7-dimethylphthalazine
(173) 1-Anilino-4-(2,4-dimethoxyphenyl)-6,7-dimethylphthalazine
(174) 1-Anilino-4-(4-chlorophenyl)-6,7-dimethylphthalazine
(175) 1-(3-Chloroanilino)-4-(4-chlorophenyl)-6,7-dimethylphthalazine
(176) 1-(3-Chloro-4-methylanilino)-4-(4-chlorophenyl)-6,7-dimethylphthalazine
(177) 1-Anilino-6,7-dimethyl-4-(4-fluorophenyl)phthalazine
(178) 1-Anilino-6,7-dimethyl-4-(4-ethoxycarbonylphenyl)phthalazine
(179) 1-Anilino-6,7-dimethoxy-4-(4-methylphenyl)phthalazine
(180) 6,7-Dimethoxy-1-(2,5-dimethylanilino)-4-(4-methylphenyl)phthalazine
(181) 6,7-Dimethoxy-1-(2,5-dimethoxyanilino)-4-(4-methylphenyl)phthalazine
(182) 1-(3-Chloroanilino)-6,7-dimethoxy-4-(4-methylphenyl)phthalazine
(183) 1-Anilino-4-(4-butylphenyl)-6,7-dimethoxyphthalazine
(184) 1-Anilino-6,7-dimethoxy-4-(4-methoxyphenyl)phthalazine
(185) 1-Anilino-6,7-dimethoxy-4-(2,4-dimethoxyphenyl)phthalazine
(186) 1-Anilino-4-(4-chlorophenyl)-6,7-dimethoxyphthalazine
(187) 1-Anilino-6,7-dimethoxy-4-(4-fluorophenyl)phthalazine
(188) 1-Anilino-6,7-dimethoxy-4-(4-ethoxycarbonylphenyl)phthalazine
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(191) 1-Anilino-6,7-dichloro-4-(4-methoxyphenyl)phthalazine
(192) 1-Anilino-4-(4-butoxyphenyl)-6,7-dichlorophthalazine
(193) 1-Anilino-6,7-dichloro-4-(2,4-dimethoxyphenyl)phthalazine
(194) 1-Anilino-4-(4-chlorophenyl)-6,7-dichlorophthalazine
(195) 1-Anilino-6,7-dichloro-4-(4-fluorophenyl)phthalazine
(196) 1-Anilino-6,7-dichloro-4-(4-ethoxycarbonylphenyl)phthalazine
(197) 1-Anilino-4-(4-carboxyphenyl)phthalazine
(198) 4-(4-Carboxyphenyl)-1-(2,5-dimethylanilino)phthalazine
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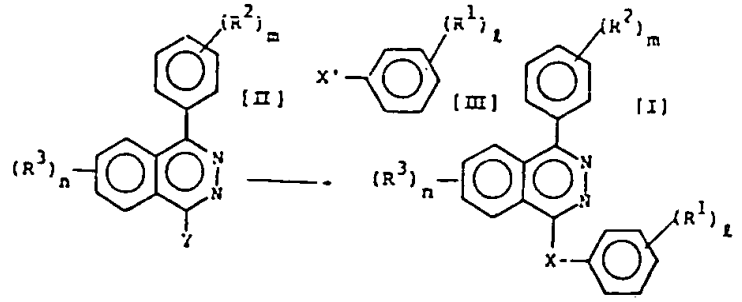
(200) 4-(4-Carboxyphenyl)-1-(3chloroanilino)phthalazine
(201) 4-(4-Carboxyphenyl)-1-(3-trifluoromethylanilino)phthalazine
(202) 4-(4-Carboxyphenyl)-1-(5-chloro-2-methoxyanilino)phthalazine
(203) 1-Anilino-4-(4-hydroxyphenyl)phthalazine
(204) 1-(2,5-Dimethylanilino)-4-(4-hydroxyphenyl)phthalazine
(205) 1-(2,5-Dimethylanilino)-4-(4-hydroxyphenyl)phthalazine
(206) 1-(3-Chloroanilino)-4-(4-hydroxyphenyl)phthalazine
(207) 4-(4-Hydroxyphenyl)-1-(3-trifluoromethylanilino)phthalazine
(208) 1-(5-Chloro-2-methoxyanilino)-4-(4-carboxyphenyl)phthalazine
(209) 1-(4-Acetylanilino)-4-(4-methylphenyl)phthalazine
(210) 1-(4-Acetylanilino)-6,7-dimethyl-4-phenylphthalazine
(211) 1-(4-Methylphenoxy)-4-phenylphthalazine
(212) 1-(3-Methylphenoxy)-4-phenylphthalazine
(213) 1-(2-Methylphenoxy)-4-phenylphthalazine
(214) 1-(4-Ethylphenoxy)-4-phenylphthalazine
(215) 1-(2-Ethylphenoxy)-4-phenylphthalazine
(216) 1-(4-n-Butylphenoxy)-4-phenylphthalazine
(217) 1-(3-Butylphenoxy)-4-phenylphthalazine
(218) 1-(4-t-Butylphenoxy)-4-phenylphthalazine
(219) 1-(4-Methoxyphenoxy)-4-phenylphthalazine
(220) 1-(3-Methoxyphenoxy)-4-phenylphthalazine
(221) 1-(3-Propoxyphenoxy)-4-phenylphthalazine
(222) 1-(3-Butoxyphenoxy)-4-phenylphthalazine
(223) 1-(4-Fluorophenoxy)-4-phenylphthalazine

(224) 1-(3-Fluorophenoxy)-4-phenylphthalazine
(225) 1-(4-Chlorophenoxy)-4-phenylphthalazine
(226) 1-(3-Chlorophenoxy)-4-phenylphthalazine
(227) 1-(2-Chlorophenoxy)-4-phenylphthalazine
(228) 1-(4-Bromophenoxy)-4-phenylphthalazine
(229) 1-(3-Bromophenoxy)-4-phenylphthalazine
(230) 1-(3-Iodophenoxy)-4-phenylphthalazine
(231) 1-(4-Ethoxycarbonylphenoxy)-4-phenylphthalazine
(232) 1-(4-Carboxyphenoxy)-4-phenylphthalazine
(233) 1-(4-Cyanophenoxy)-4-phenylphthalazine
(234) 1-(4-Acetylphenoxy)-4-phenylphthalazine
(235) 1-(4-Trifluoromethylphenoxy)-4-phenylphthalazine
(236) 1-(3-Trifluoromethylphenoxy)-4-phenylphthalazine
(237) 1-(3-Hydroxyphenoxy)-4-phenylphthalazine
(238) 1-(2,3-Dimethylphenoxy)-4-phenylphthalazine
(239) 1-(2,5-Dimethylphenoxy)-4-phenylphthalazine
(240) 1-(2,5-Diethylphenoxy)-4-phenylphthalazine
(241) 1-(2,5-Dipropylphenoxy)-4-phenylphthalazine
(242) 1-(2,5-Dimethoxyphenoxy)-4-phenylphthalazine
(243) 1-(3,4-Dimethoxyphenoxy)-4-phenylphthalazine
(244) 1-(2,5-Dichlorophenoxy)-4-phenylphthalazine
(245) 1-(2,6-Dichlorophenoxy)-4-phenylphthalazine
(246) 1-(2,5-Difluorophenoxy)-4-phenylphthalazine
(247) 1-(3-Chloro-4-methylphenoxy)-4-phenylphthalazine
(248) 1-(3-Methyl-4-chlorophenoxy)-4-phenylphthalazine
(249) 1-(3-Fluoro-4-methylphenoxy)-4-phenylphthalazine
(250) 1-(2-Methoxy-4-chlorophenoxy)-4-phenylphthalazine
(251) 1-(2-Methoxy-5-methylphenoxy)-4-phenylphthalazinee
(252) 1-(2-Methyl-4-trifluoromethylphenoxy)-4-phenylphthalazine
(253) 1-(2,4,6-Trimethylphenoxy)-4-phenylphthalazine

Process for preparation of the compound (I)

The compound represented by the formula [I] can be prepared according to any suitable process, which is not particularly limited. Preferably, however, the compound (I) can be synthesized by the following reaction route:



In the above formulae, X' represents $-NH_2$ or OH; Y a halogen atom (e.g., chlorine, bromine or iodine), a group of the formula: $-S(O)_p-R^4$ (p=0—2, R^4 is a C_{1-5} alkyl, phenyl or a substituted phenyl) or a group of the formula: $-OR^5$ (R^5 is a C_{1-5} alkyk, phenyl or a substituted phenyl); and all of the other symbols have the same meanings as defined above.

According to this process, the starting compound represented by the formula (II), namely 1-chloro-4-phenylphthalazine or its derivative, is allowed to react with a benzene derivative represented by the formula (III), in either the presence or absence of a solvent, preferably in the presence of a catalyst, to prepare a 4-phenylphthalazine derivative represented by the formula [I].

The starting materials, i.e., 1-choloro-4-phenylphthalazine [II] or derivatives thereof were synthesized according to the method as described in Journal of Pharmacology *86*, 576 (1966) or the methods similar thereto.

As the benzene derivative [III] to be reacted with the compound (II) as mentioned above, there may be employed suitable substituted anilines or substituted phenols.

The reaction temperature may be in the range from −20 to 250°C., preferably from −10 to 180°C. The reaction time may be from 5 minutes to 24 hours, preferably from 10 minutes to 10 hours.

When a catalyst is to be employed, there may be used an organic base such as ammonia, triethylamine, piperidine or pyridine, or an inorganic base such as sodium carbonate, potassium

carbonate, sodium hydroxide, potassium hydroxide, sodium hydride or sodium amide may be added at a molar ratio relative to the compound (II) in the range from 0.5 to 5, preferably from 1 to 3. Alternatively, it is also possible to use a metal such as copper, magnesium, cadmium, sodium or potassium, at a molar ratio relative to the compound (II) in the range from 0.001 to 2, preferably from 0.01 to 1.5.

When a solvent is to be employed, there may be used a solvent selected from ethers such as ethyl ether, tetrahydrofuran, and dioxane; halogenated alkanes such as chloroform, methylene chloride, etc.; alcohols such as methanol, ethanol, etc.; aromatic hydrocarbons such as benzene, toluene, xylene, etc.; amides such as demethylformamide, dimethylacetamide, etc.; and dimethylsulfoxide; and so on.

The compound (III) may be used in an amount of 0.5 to 30 moles, preferably 1 to 20 moles, per mole of the compound (II).

After completion of the reaction, the reaction mixture may be poured into a large excess of water or dissolved as such in a solvent such as chloroform to be neutralized therein. If desired, the precipitated crystals may be collected by filtration after concentration, or alternatively the product may be extracted with a suitable solvent such as chloroform when there is no precipitation, followed by recrystallization or chromatography according to conventional procedures.

The present invention is further illustrated by the following Examples, by which the present invention is not limited.

EXAMPLE 1

Synthesis of 1-(4-methylanilino)-4-phenylphthalazine (Compound No. 1)

To 2.41 g of 1-chloro-4-phenylphthalazine, there were added 5.35 g of p-toluidine and 70 mg of copper powders. The mixture was then subjected to stirring under heating for one hour while maintaining the reaction temperature at 100°C. After the reaction mixture was left to cool, a large excess of chloroform was added thereto. The resultant insolubles were filtered off and the filtrate was washed with a 5% aqueous sodium hydroxide and then with water. The organic layer was dried and concentrated, and the residue was recrystallized from ethanol to give 910 mg (yield: 29%) of pale yellow crystals.

m.p.:	185—186°C.
I.R.:	1630 cm^{-1}, 1510 cm^{-1}, 1410 cm^{-1}
M.S.:	310 (M^+—1)

EXAMPLES 2—30

The compounds as shown in Table 1 were synthesized according to the methods similar to Example 1.

TABLE 1

Example	Compound No.	m.p./°C	I R/cm^{-1}	M.S.
2	(2)	202 ~ 203	3270, 1575, 1520 1410, 790	310 ($M^{\pm}1$)
3	(3)	188	3200, 1500, 1400 1200, 755	311 (M^{+}) 296
4	(4)	206 ~ 207	2990, 1625, 1520 1420, 780	324 ($M^{\pm}1$)
5	(6)	189 ~ 190	2860, 1620, 1520 1420, 780	353 (M^{+}) 310
6	(9)	206 ~ 207.5	2950, 1640, 1510 1420, 1240, 785	327 (M^{+}) 312
7	(10)	196	3000, 1610, 1500 1400, 1155, 780	326 ($M^{\pm}1$)
8	(12)	168.5 ~ 169	2950, 1620, 1505 1410, 1240, 790	369 (M^{+}) 312
9	(13)	206 ~ 207	3050, 1620, 1520 1410, 1220, 780	314 ($M^{\pm}1$)
10	(14)	239 ~ 240	3280, 1620, 1520 1400, 1140, 790	314 ($M^{\pm}1$)
11	(16)	193 ~ 194	1620, 1580, 1500 1400, 820, 770	330 332 } (M^{+})
12	(17)	191 ~ 194	1600, 1510, 1420 1390, 770	330 332 } (M^{+})
13	(18)	170 ~ 171.5	3440, 1600, 1520 1400, 1040, 760	330 332 } (M^{+})
14	(19)	219 ~ 222	3000, 1625, 1510 1400, 820, 760	376 374 } ($M^{\pm}1$)
15	(23)	236 ~ 237.5	3000, 1720, 1615 1520, 1410, 1280	369 368 } (M^{+})
16	(25)	240 ~ 242.5	3360, 2210, 1610 1510, 14[illegible], 790	321 ($M^{\pm}1$)
17	(26)	247 ~ 248.5	3400, 1680, 1600 1520, 1400, 1280	338 ($M^{\pm}1$)
18	(28)	174 ~ 175.5	3040, 1630, 1520 1410, 1340, 1100	364 ($M^{\pm}1$)

TABLE 1 (Continued)

Example	Compound No.	m.p./°C	I.R./cm^{-1}	M.S.
19	(31)	240 ~ 242	3200, 1520, 1415 790, 770	325 (M^+) 310
20	(32)	206.5 ~ 207.5	3400, 1500, 1400 810, 780	325 (M^+) 310
21	(33)	202 ~ 203.5	3200, 1500, 1400 810, 780	325 (M^+) 310
22	(34)	204 ~ 204.5	3200, 1510, 1420 790, 770	324 (M^+-1)
23	(37)	215 ~ 216	3440, 1610, 1520 1430, 790	357 (M^+) 326
24	(43)	217	1590, 1510, 1410 780, 700	347 345 } (M^+)
25	(44)	232 ~ 232.5	3400, 1490, 1400 820, 780, 700	347 345 } (M^+)
26	(42)	171 ~ 172	3000, 1610, 1500 1400, 775, 700	346 344 } (M^+-1)
27	(47)	129 ~ 132	3450, 1530, 1430 1230, 790, 710	341 (M^+) 310
28	(48)	74.5 ~ 75	1600, 1500, 1420 1220, 790, 780	364 362 } (M^+)
29	(51)	200 ~ 202.5	3200, 1500, 1400 780, 700	339 (M^+)
30	(24)	250<	3360, 1680, 1600 1520, 1410, 780	340 (M^+-1)

EXAMPLE 31

Synthesis of 1-(2-methylphenoxy)-4-phenylphthalazine (Compound No. 213)

To 1.20 g of 1-chloro-4-phenylphthalazine, there were added 5.40 g of o-cresol and 360 mg of potassium hydroxide. The resultant mixture was subjected to stirring under heating for 2 hours, while maintaining the reaction temperature at 100°C. After the reaction mixture was poured into 12 ml of an aqueous solution having 3.6 g of potassium hydroxide dissolved therein, the crystals precipitated were recovered by filtration. The crude crystals were dissolved in chloroform, washed with water, dried and concentrated. Thea residue was recrystallized from ethanol-n-hexane to give 725 mg (yield: 46%) of white crystals.

m.p.: 136.5—137.5°C.
I.R.: 1490 cm^{-1}, 1385 cm^{-1}, 1230 cm^{-1}, 1190 cm^{-1}, 790 cm^{-1}, 750 cm^{-1}.
M.S.: 312 (M^+)

EXAMPLES 32—44

According to procedures similar to that as described in Example 31, there were synthesized the compounds as shown in Table 2.

TABLE 2

Example	Compound No.	m.p./°C	I R/cm ^{1}	M.S.
32	(212)	148 ~ 150	1490, 1390, 1250 1165, 800, 770	312 (M^+) 295
33	(214)	171.5 ~ 172	1510, 1385, 1210 850, 770, 700	326 (M^+) 311
34	(218)	211 ~ 212.5	2970, 1500, 1390 1230, 790	354 (M^+) 339
35	(219)	163 ~ 164	1510, 1390, 1205 1030, 850, 700	328 (M^+) 121
36	(227)	171 ~ 172	1550, 1480, 1380 1230, 790, 780	331 297 } ($M^{\pm}1$)
37	(228)	179 ~ 180	1490, 1380, 1220 1010, 790	376 378 } (M^+)
38	(234)	139 ~ 141.5	1700, 1600, 1380 1220, 850, 800	340 325 } (M^+)
39	(236)	119 ~ 121	1450, 1385, 1330 1170, 1120, 900	366 (M^+) 365
40	(226)	149 ~ 149.5	1595, 1380, 1220 890, 795, 700	332 334 } (M^+)
41	(239)	153 ~ 155	1570, 1385, 1250 1120, 770	326 (M^+) 309
42	(248)	155.5 ~ 156	1480, 1390, 1240 1170, 1050, 790	346 348 } (M^+)
43	(244)	175.5 ~ 176.5	1590, 1470, 1365 1220, 1090, 770	365 ($M^{\pm}1$) 331
44	(245)	210 ~ 210.5	1450, 1380, 1360 1240, 770	366 (M^+) 331

EXAMPLE 45

Synthesis of 1-(3-chloroanilino)-4-(4-methylphenyl)phthalazine (Compound No. 60)

To 172 mg of 1-chloro-4-(4-methylphenyl)phthalazine, there was added 319 mg of m-chloroaniline, and the resultant mixture was heated at 100°C with stirring for one hour. After the reaction mixture was left to cool to room temperature, a large excess of chloroform was added thereto, followed by washing with a 5% aqueous sodium hydroxide and then with water. The organic layer was dried and subjected to concentration. The residue was recrystallized from ethanol to give 145 mg (yield: 62%) of pale yellow crystals.

m.p.: 211.5—212°C.
I.R.: 595 cm^{-1}, 1510 cm^{-1}, 1475 cm^{-1}, 1405 cm^{-1}, 770 cm^{-1}.
M.S.: 345 (M^+), 343 (M^+), 344.

EXAMPLES 46—109

The compounds as shown in Table 3, having the following formula:

TABLE 2

Example	Compound No.	m.p./°C	I R/cm ^{1}	M.S.
32	(212)	148 ~ 150	1490, 1390, 1250 1165, 800, 770	312 (M^+) 295
33	(214)	171.5 ~ 172	1510, 1385, 1210 850, 770, 700	326 (M^+) 311
34	(218)	211 ~ 212.5	2970, 1500, 1390 1230, 790	354 (M^+) 339
35	(219)	163 ~ 164	1510, 1390, 1205 1030, 850, 700	328 (M^+) 121
36	(227)	171 ~ 172	1550, 1480, 1380 1230, 790, 780	331 297 }($M^{\pm}1$)
37	(228)	179 ~ 180	1490, 1380, 1220 1010, 790	376 378 }(M^+)
38	(234)	139 ~ 141.5	1700, 1600, 1380 1220, 850, 800	340 325 }(M^+)
39	(236)	119 ~ 121	1450, 1385, 1330 1170, 1120, 900	366 (M^+) 355
40	(226)	149 ~ 149.5	1595, 1380, 1220 890, 795, 700	332 334 }(M^+)
41	(239)	153 ~ 155	1570, 1385, 1250 1120, 770	326 (M^+) 309
42	(248)	155.5 ~ 156	1480, 1390, 1240 1170, 1050, 790	346 348 }(M^+)
43	(244)	175.5 ~ 176.5	1580, 1470, 1355 1220, 1090, 770	365 ($M^{\pm}1$) 331
44	(245)	210 ~ 210.5	1450, 1380, 1360 1240, 770	366 (M^+) 331

EXAMPLE 45

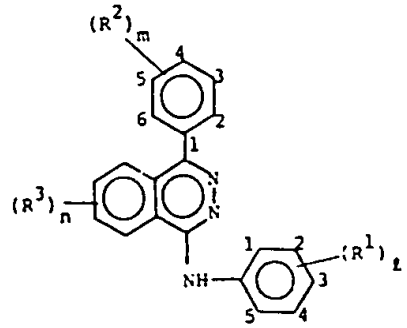
Synthesis of 1-(3-chloroanilino)-4-(4-methylphenyl)phthalazine (Compound No. 60)

To 172 mg of 1-chloro-4-(4-methylphenyl)phthalazine, there was added 319 mg of m-chloroaniline, and the resultant mixture was heated at 100°C with stirring for one hour. After the reaction mixture was left to cool to room temperature, a large excess of chloroform was added thereto, followed by washing with a 5% aqueous sodium hydroxide and then with water. The organic layer was dried and subjected to concentration. The residue was recrystallized from ethanol to give 145 mg (yield: 62%) of pale yellow crystals.

m.p.: 211.5—212°C.
I.R.: 595 cm^{-1}, 1510 cm^{-1}, 1475 cm^{-1}, 1405 cm^{-1}, 770 cm^{-1}.
M.S.: 345 (M^+), 343 (M^+), 344.

EXAMPLES 46—109

The compounds as shown in Table 3, having the following formula:



were prepared according to the procedures similarly as described in Example 45.

TABLE 3

Example	Compound No.	R^1	R^2	R^3	m.p./°C	I.R./cm^{-1}	MS
46	(63)	3–CF_3	4–CH_3	H	179–180	3240, 1595, 1510 1400, 1330, 1160	379 (M^+) 378
47	(56)	2–CH_3, 5–CH_3	4–CH_3	H	184–185	3200, 1610, 1490 1405, 1020	339 (M^+) 324
48	(59)	2–OCH_3, 5–OCH_3	4–CH_3	H	192.5–193	3435, 1600, 1510 1420, 1200, 1035	371 (M^+) 340
49	(64)	2–OCH_3, 4–Cl	4–CH_3	H	197–197.5	3430, 1595, 1510 1420, 1240, 1010	377 (M^+) 375 (M^+)
50	(78)	3–Cl	4–OCH_3	H	227–228	1600, 1480, 1400 1250, 770	363 (M^+) 361 (M^+) 360
51	(79)	3–CF_3	4–OCH_3	H	228–229	3230, 1610, 1515 1405, 1335, 1250	395 (M^+) 394
52	(76)	2–CH_3, 5–CH_3	4–OCH_3	H	179–180	1610, 1490, 1400 1250, 1175	355 (M^+) 340
53	(77)	2–OCH_3, 5–OCH_3	4–OCH_3	H	185–186	3435, 1610, 1515 1250, 1020	387 (M^+) 356
54	(80)	2–OCH_3, 4–Cl	4–OCH_3	H	206–207	3435, 1600, 1515 1420, 1250, 1020	393 (M^+) 391 (M^+)
55	(97)	3–Cl	4–Cl	H	222–223	1600, 1480, 1410 1080, 780	367 (M^+) 365 (M^+) 364

TABLE 3 (Continued)

Example	Compound No.	R^1	R^2	R^3	m.p./°C	I.R./cm^{-1}	MS
56	(98)	3–CF_3	4–Cl	H	180–181	3270, 1605, 1450 1415, 1340, 1120	401 (M^+) 399 (M^+) 398
57	(95)	2–CH_3, 5–CH_3	4–Cl	H	196–197	1580, 1500, 1410 1090, 835	361 (M^+) 359 (M^+) 344
58	(96)	2–OCH_3, 5–OCH_3	4–Cl	H	190–192	3440, 1600, 1510 1430, 1220, 1045	393 (M^+) 391 (M^+) 360
59	(99)	2–OCH_3, 4–Cl	4–Cl	H	200–201	3420, 1600, 1410 1420, 1250	397 (M^+) 395 (M^+) 364
60	(70)	3–Cl	4–C_6H_5	H	193–194	2920, 1600, 1410 900, 770	389 (M^+) 387 (M^+) 386
61	(71)	3–CF_3	4–C_6H_5	H	164–167	2920, 1610, 1410 1330, 1170, 1120	421 (M^+) 420
62	(68)	2–CH_3, 5–CH_3	4–C_6H_5	H	169.5–171	2920, 1610, 1490 1400, 805, 775	381 (M^+) 366
63	(69)	2–OCH_3, 5–OCH_3	4–C_6H_5	H	159.5–160	2920, 1610, 1520 1430, 1205, 785	413 (M^+) 382
64	(72)	2–OCH_3, 5–Cl	4–C_6H_5	H	173.5–174.5	3440, 2920, 1595 1510, 1420, 1250	419 (M^+) 417 (M^+) 396

TABLE 3 (Continued)

Example	Compound No.	R^1	R^2	R^3	m.p./°C	I.R./cm^{-1}	MS
65	(85)	3–Cl	4–OC_4H_9	H	184.5–185.5	2950, 1600, 1515 1420, 1250, 770	405 (M^+) 403 (M^+) 402
66	(86)	3–CF_3	4–OC_4H_9	H	183–184	2950, 1610, 1510 1400, 1330, 1110	437 (M^+) 438
67	(83)	2–CH_3, 5–CH_3	4–OC_4H_9	H	156.5–158	2950, 1610, 1500 1400, 1250	397 (M^+) 382
68	(84)	2–OCH_3, 5–OCH_3	4–OC_4H_9	H	163–163.5	3440, 2950, 1605 1505, 1240	429 (M^+) 398
69	(87)	2–OCH_3 5–Cl	4–OC_4H_9	H	181.5–182.5	3420, 2950, 1600 1510, 1410, 1250	435 (M^+) 433 (M^+) 402
70	(104)	3–Cl	4–F	H	228.5–229.5	1600, 1515, 1420 1220, 1150, 775	351 (M^+) 349 (M^+) 348
71	(105)	3–CF_3	4–F	H	205–206.5	1610, 1520, 1420 1335, 1120, 800	383 (M^+) 382
72	(102)	2–CH_3 5–CH_3	4–F	H	188.5–189.5	1600, 1500, 1415 1225	343 (M^+) 328
73	(103)	2–OCH_3 5–OCH_3	4–F	H	176–177	3445, 1600, 1510 1430, 1210, 1020	375 (M^+) 344
74	(106)	2–OCH_3 5–Cl	4–F	H	216–217	3445, 1600, 1515 1430, 1240, 1015	381 (M^+) 379 (M^+) 348

TABLE 3 (Continued)

Example	Compound No.	R^1	R^2	R^3	m.p./°C	I.R./cm^{-1}	MS
75	(91)	3–Cl	2–OCH_3, 4–OCH_3	H	200–201.5	1600, 1485, 1400 1215, 1160, 775	393 (M^+) 391 (M^+)
76	(92)	3–CF_3	2–OCH_3, 4–OCH_3	H	213–214	1620, 1500, 1400 1340, 1215, 1110	425 (M^+) 394
77	(89)	2–CH_3 5–CH_3	2–OCH_3 4–OCH_3	H	220–221.5	1615, 1505, 1410 1215, 1160, 1040	385 (M^+) 370
78	(90)	2–OCH_3 5–OCH_3	2–OCH_3 4–OCH_3	H	177–177.5	3440, 1615, 1515 1210, 1030	417 (M^+) 386
79	(93)	2–OCH_3, 5–Cl	2–OCH_3, 4–OCH_3	H	203.5–205	3450, 1600, 1510 1420, 1210, 1030	392 (M–1) 390 (M–1)
80	(110)	3–Cl	4–COOEt	H	173–174	1710, 1590, 1500 1410, 1270, 770	405 (M^+) 403 (M^+) 402
81	(111)	3–CF_3	4–COOEt	H	215.5–216.5	1710, 1625, 1495 1400, 1330, 1270	437 (M^+) 436
82	(108)	2–CH_3, 5–CH_3	4–COOEt	H	201.5–202.5	3300, 1710, 1480 1400, 1270, 1100	397 (M^+) 382
83	(109)	2–OCH_3 5–OCH_3	4–COOEt	H	198–199.5	3440, 1725, 1600 1560, 1270, 1090	429 (M^+) 398
84	(112)	2–OCH_3, 5–Cl	4–COOEt	H	206–207.5	3435, 1725, 1600 1510, 1420, 1270	435 (M^+) 433 (M^+) 402

TABLE 3 (Continued)

Example	Compound No.	R^1	R^2	R^3	m.p./°C	I.R./cm^{-1}	MS
85	(119) (120)	3–Cl	H	6–CH_3 7–CH_3 } mix	221–223	1590, 1475, 1400 1250, 770	347 (M^+) 345 (M^+) 344
86	(121) (122)	3–CF_3	H	6–CH_3 7–CH_3 } mix.	221–222.5	1600, 1440, 1400 1330, 1150, 1110	379 (M^+) 378
87	(115) (116)	2–CH_3, 5–CH_3	H	6–CH_3 7–CH_3 } mix.	164–168	1620, 1500, 1410 800	339 (M^+) 324
88	(117) (118)	2–OCH_3, 5–OCH_3	H	6–CH_3 7–CH_3 } mix.	192–193	3430, 1600, 1520 1450, 1210, 1035	371 (M^+) 340
89	(123) (124)	2–OCH_3, 5–Cl	H	6–CH_3 7–CH_3 } mix.	146–147.5	3430, 1600, 1510 1420, 1240, 1210	377 (M^+) 375 (M^+) 344
90	(125)	H	H	6–CH_3, 7–CH_3	238–239	1605, 1500, 1410 750	325 (M^+) 324
91	(126)	3–Cl	H	6–CH_3 7–CH_3	243.5–244.5	1605, 1500, 1400 775, 765	361 (M^+) 359 (M^+) 358
92	(131)	3–CF_3	H	6–CH_3, 7–CH_3	255–256	1615, 1570, 1445 1420, 1330, 1170	393 (M^+) 392
93	(127)	2–CH_3, 5–CH_3	H	6–CH_3, 7–CH_3	153.5–156	1600, 1575, 1440 810, 770	353 (M^+) 338
94	(128)	2–OCH_3, 5–OCH_3	H	6–CH_3, 7–CH_3	232–233	3450, 1610, 1520 1400, 1220, 1010	385 (M^+) 354

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TABLE 3 (Continued)

Example	Compound No.	R^1	R^2	R^3	m.p./°C	I.R./cm^{-1}	MS
95	(132)	2–OCH_3, 5–Cl	H	6–CH_3, 7–CH_3	237–238	3450, 1600, 1520 1425, 1250, 1020	391 (M^+) 389 (M^+) 358
96	(138)	H	H	6–OCH_3, 7–OCH_3	205.5–207	1620, 1500, 1410 1220, 1100, 750	357 (M^+) 356
97	(141)	3–Cl	H	6–OCH_3, 7–OCH_3	199.5–204	1620, 1600, 1520 1410, 1220, 775	393 (M^+) 391 390
98	(142)	3–CF_3	H	6–OCH_3, 7–OCH_3	223–226	1610, 1510, 1400 1330, 1155, 1115	425 (M^+) 424
99	(139)	2–CH_3, 5–CH_3	H	6–OCH_3, 7–OCH_3	192–193.5	1610, 1510, 1410, 1250, 1210	385 (M^+) 370
100	(140)	2–OCH_3, 5–OCH_3	H	6–OCH_3, 7–OCH_3	158–158	3440, 1610, 1510 1410, 1215, 1080	417 (M^+) 386
101	(143)	2–OCH_3, 5–Cl	H	6–OCH_3, 7–OCH_3	211.5–213	3440, 1610, 1590 1510, 1410, 1240	423 (M^+) 421 (M^+) 390
102	(144)	4–C_4H_9	H	6–OCH_3, 7–OCH_3	187.5–189	2920, 1615, 1495 1405, 1240, 1090	413 (M^+) 412
103	(145)	4–OC_4H_9	H	6–OCH_3, 7–OCH_3	183.5–186	2940, 1615, 1500 1405, 1220, 825	429 (M^+) 372
104	(151)	3–Cl	H	6–Cl, 7–Cl	248–250	1600, 1480, 1405 1090, 890, 760	403 (M^+) 402 (M^+) 401 (M^+) 400

TABLE 3 (Continued)

Example	Compound No.	R^1	R^2	R^3	m.p./°C	I.R./cm^{-1}	MS
105	(152)	3-CF_3	H	6-Cl, 7-Cl	243-244.5	1610, 1515, 1450 1415, 1335, 1110	435 (M^+) 434 (M^+) 433 (M^+) 432
106	(149)	2-CH_3, 5-CH_3	H	6-Cl, 7-Cl	204-205.5	1605, 1560, 1495 1400, 1380	395 (M^+) 393 (M^+)
107	(150)	2-OCH_3, 5-OCH_3	H	6-Cl, 7-Cl	199.5-201	3435, 1610, 1560 1460, 1210	427 (M^+) 425 (M^+) 394
108	(153	2-OCH_3, 5-Cl	H	6-Cl, 7-Cl	201-202	3435, 1600, 1550, 1500, 1420, 1250	431 (M^+) 429 (M^+) 400
109	(202)	2-OCH_3, 5-Cl	4-COOH	H	274-275.5	3440, 1690, 1600 1510, 1420, 1240	405 (M^+) 374

Pharmacological tests:

Artery blood of a rabbit was subjected to centrifugation to obtain platelet rich plasma. To an aliquot of 250 μl of the plasma, there was added 5 μl of each pharmaceutical solution. After incubation for two minutes, platelet aggregation was induced by adding 3 μg of collagen to the mixture. The change in platelet aggregationn was monitored and recorded by means of an aggregometer for 10 minutes.

The platelet aggregation inhibitory percentage was calculated by the following formula:

$$\text{Inhibitory percentage} = \frac{T_c - T_s}{T_c} \times 100$$

wherein T_c is the degree of aggregation when only a solvent is added and T_s is that when a pharmaceutical solution is added.

Table 4 shows inhibitory percentages at indicated mole concentrations for each compound. As apparently seen from the results, among these compounds, the anilinophthalazine derivatives are generally found to have more potent activity than the phenoxyphthalazine derivatives.

TABLE 4

Example	Compound No.	Mole concentration	
		3×10^{-6}	10^{-5}
1	(1)	56.5	33.9
2	(2)	80.6	66.1
3	(3)	100	60.9
4	(4)	100	100
5	(6)	100	100
6	(9)	76.6	39.1
7	(10)	100	100
8	(12)	100	100
9	(13)	100	100
10	(14)	100	100
11	(16)	100	36.8
12	(17)	100	100
13	(18)	100	100
14	(19)	100	100
15	(23)	65.5	50.9
16	(25)	13.6	–
17	(26)	100	21.1
18	(28)	100	100
19	(31)	82.5	24.6
20	(32)	100	45.3
21	(33)	100	100
22	(34)	100	100
23	(37)	100	100
24	(43)	100	100
25	(44)	85.5	56.5
26	(42)	100	100
27	(47)	100	100
28	(48)	100	100

TABLE 4 (Continued)

Example	Compound No.	Mole concentration	
		3×10^{-6}	10^{-6}
29	(51)	100	100
30	(24)	13.4	–
31	(213)	100	100
32	(212)	100	51.3
33	(214)	100	30.4
34	(218)	6.38	9.6
35	(219)	100	100
36	(227)	73.4	23.8
37	(228)	100	28.9
38	(234)	104	[illegible]
39	(236)	100	100
40	(226)	100	100
41	(239)	100	100
42	(248)	100	25.5
43	(244)	68.4	26.3
44	(245)	84.1	15.9
45	(60)	100	100
46	(63)	100	100
47	(56)	100	7.6
48	(59)	100	100
49	(64)	100	100
50	(78)	100	100
51	(79)	100	100
52	(76)	33.6	11.8
53	(77)	100	100
54	(80)	100	100
55	(97)	100	100
56	(98)	100	100

TABLE 4 (Continued)

Example	Compound No.	Mole concentration	
		3×10^{-6}	10^{-5}
57	(95)	58.7	15.1
58	(96)	100	9.2
59	(99)	100	100
60	(70)	28.0	23.4
61	(71)	100	26.2
62	(68)	55.9	
63	(69)	100	100
64	(72)	100	54.9
65	(85)	30.5	18.3
66	(86)	48.2	25.9
67	(83)	27.9	
68	(84)	100	100
69	(87)	61.2	35.8
70	(104)	100	66.7
71	(105)	100	74.1
72	(102)	100	69.8
73	(103)	100	91.9
74	(106)	84.4	50.0
75	(91)	92.6	10.6
76	(92)	29.7	
77	(89)	100	84.9
78	(90)	30.5	11.9
79	(93)	17.7	
80	(110)	12.0	
81	(111)	48.2	36.5
82	(108)	30.5	4.3
83	(109)	100	100
84	(112)	100	100

TABLE 4 (Continued)

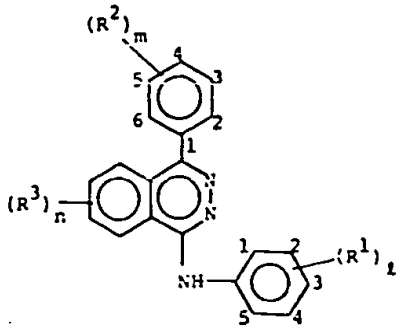
Example	Compound No.	Mole concentration		
		10^{-5}	3×10^{-6}	10^{-6}
85	(119) (120)		100	100
86	(121) (122)		93.1	34.5
87	(115) (116)		100	100
88	(117) (118)		100	100
89	(123) (124)		100	100
90	(125)			100
91	(130)			100
92	(131)			100
93	(127)		100	23.1
94	(128)			100
95	(132)			100
96	(138)			9.1
97	(141)	10.7		
98	(142)	46.3		
103	(145)			8.9
104	(151)	13.3		
105	(152)		100	15.2
107	(150)	15.8		
108	(153)	27.6		

Safety

Each of the compounds according to the present invention was found to be very low in toxicity, namely not less than 5000 mg/Kg in terms of LD_{50} as measured by oral administration for mouse.

CLAIMS

1. A 4-phenylphthalazine derivative represented by the following formula or a pharmaceutically acceptable salt thereof:



wherein X stands for NH or O; R^1 an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a halogen atom, an alkoxycarbonyl group having 2 to 6 total carbon atoms, a carboxyl group, a cyano group, an alkylcarbonyl group having 2 to 4 total carbon atoms, a hydroxyl group or a trifluoromethyl group; R^2 and R^3, which may be identical or different (may also be the same as or different from R^1), each represent an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a halogen atom, an alkoxycarbonyl group having 2 to 6 total carbon atoms, a carboxyl group, an alkylcarbonyl group having 2 to 4 total carbon atoms, a hydroxyl group or a *trifluoropmethyl group; and each of l, m and n is an integer of zero to 3 (provided that: l*=1 to 3 and m=n=zero when X is O, and the case where l=m=n=zero is excluded when X is NH), each plural number of R^1, R^2 and R^3 being identical or different when the integers l, m and n are two or more.

2. A 4-phenylphthalazine derivative according to Claim 1, wherein X is NH.

3. A 4-phenylphthalazine derivative according to Claim 2, wherein l, m and n are one combination selected from the following combinations (1) to (4):

(1) l=1 to 3, m=n=zero;
(2) l=1 to 2, m=1 to 2, n=zero;
(3) l=1 to 2, m=zero, n=1 to 2; and
(4) l=m=zero, n=1 to 2.

4. A 4-phenylphthalazine derivative according to Claim 3, wherein l=1 to 3 and m=n=zero.

5. A 4-phenylphthalazine derivative according to Claim 3, wherein l=1 to 2, m=1 to 2 and n=zero.

6. A 4-phenylphthalazine derivative according to Claim 3, wherein l=1 to 2, m=zero and n=1 to 2.

7. A 4-phenylphthalazine derivative according to Claim 3, wherein l=m=zero and n=1.

8. A 4-phenylphthalazine derivative according to Claim 1, wherein X is O.

9. A 4-phenylphthalazine derivative according to Claim 8, wherein l=1 to 3 and m=n=zero.

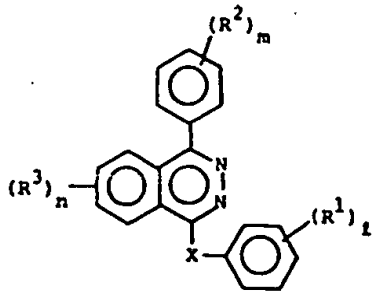
10. A 4-phenylphthalazine derivative according to Claim 9, wherein l=1 to 2.

11. A 4-phenylphthalazine derivative according to Claim 1, wherein R^1 is an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, a halogen atom or a trifluormethyl group.

12. A 4-phenylphthalazine derivative according to Claim 1, wherein R^2 is an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms or a halogen atom.

13. A 4-phenylphthalazine derivative according to Claim 1, wherein R^3 is an alkyl group.

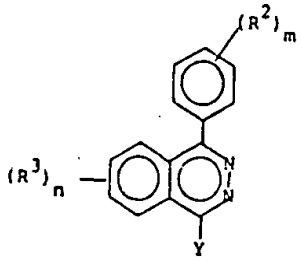
14. A process for preparing a 4-phenylphthalazine derivative represented by the following formula:



wherein X stands for NH or O; R^1 an alkyl group having 1 to 5 carbon atoms, an alkoxyy group having 1 to 5 carbon atoms, a halogen atom, an alkoxycarbonyl group having 2 to 6 total carbon atoms, a carboxyl group, a cyano group, an alkylcarbonyl group having 2 to 4 total carbon atoms, a hydroxyl group or a trifluoromethyl group; R^2 and R^3, which may be identical or different (may also be the same as or different from R^1), each represent an alkyl group having 1 to 5 carbon atoms, an

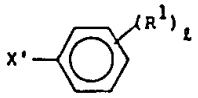
alkoxy group having 1 to 5 carbon atoms, a halogen atom, an alkoxycarbonyl group having 2 to 6 total carbon atoms, a carboxyl group, an alkylcarbonyl group having 2 to 4 total carbon atoms, a hydroxyl group or a trifluoromethyl group; and each of l, m and n is an integer of zero to 3 (provided that l=1 to 3 and m=n=zero when X is O, and the case where l=m=n=zero is excluded when X is NH), each plural number of R^1, R^2 and R^3 being identical or different when the integers l, m and n are two or more,

which comprises allowing a compound of the formula:



Y represents a halogen atom, a group of the formula: $—S(O)_p—R^4$, in which p=0—2, R^4 is a C_{1-5} alkyl, phenyl or a substituted phenyl or a group of the formula: $—OR^5$, in which R^5 is a C_{1-5} alkyl, phenyl or a substituted phenyl; R^2, R^3, m and n have the same meanings as defined above,

to react with a compound of the formula:



wherein X' represents $—NH_2$ of OH, and R^1 and l have the same meanings as defined above.

15. A process as claimed in Claim 14 and substantially as hereinbefore described with reference to Examples 1 to 109.

16. 4-phenylphthalazine derivatives when prepared by a process as claimed in Claim 14 or 15.

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ST segment change in the same model, and it improved acute myocardial ischemia in anesthetized dogs with partially occluded coronary arteries by dilating the large conductive coronary artery (Isono et al., 1993b). This evidence regarding the action of these guanylate cyclase activators and the finding that E4021 relaxes isolated coronary arteries, as noted previously by Saeki et al. (1993), seem to support the possibility outlined above.

Other mechanisms underlying the action of E4021 on myocardial ischemia may be related to the reduction in the heart preload and afterload. It is well established that nitro vasodilators induce venodilatation, with a consequent reduction of left ventricular end-diastolic pressure and end-diastolic volume (Silber, 1990). FK409 decreases venous return in anesthetized dogs (Yamada et al., 1991). Zaprinast was shown to attenuate ST segment elevation on the electrocardiogram and the increase in left ventricular end-diastolic pressure induced by ventricular overdrive pacing in conscious rabbits (Szilvassy et al., 1993). This result suggests that the protective effect of the phosphodiesterase type V inhibitor on myocardial ischemia may be associated with a decrease in preload. We observed that E4021, like isosorbide dinitrate, causes a dose-dependent reduction in left ventricular end-diastolic pressure in anesthetized dogs (unpublished data). The decreased venous return after E4021 administration leads to reduced cardiac size and work. In the present study, we also found that E4021 decreased mean arterial pressure in a dose-dependent fashion, indicating a reduction in afterload. The decreased preload and afterload may improve myocardial ischemia, as a consequence of lowering the oxygen requirement of the heart. However, we have no decisive evidence concerning the cardiohemodynamic mechanism that underlies the ameliorating action of E4021 on myocardial ischemia in the present experimental models.

In conclusion, the results of the present studies suggest that E4021 may be useful in the treatment of angina pectoris, as a drug to be administered orally like the nitro vasodilators. Nitro vasodilators, however, despite being very effective for the treatment of ischemic heart disease, exhibit the serious problem of clinically attenuating the antianginal effect, i.e., tolerance develops (Leier, 1985). This tolerance may be related to the guanylate cyclase activation pathway (Ignarro et al., 1981). Saeki et al. (1993) have shown that E4021 does not affect guanylate cyclase activity. We would therefore expect that the phosphodiesterase type V inhibitor would have an advantage over nitro vasodilators in this regard. In any case, further investigations are necessary to clarify the mechanism responsible for the anti-ischemic action of E4021 and to determine the clinical effectiveness of this drug in the treatment of ischemic heart disease and other conditions.

References

Ahn, H.S., W. Crim, B. Pitts and E.J. Sybertz, 1992, Calcium-calmodulin-stimulated and cyclic-GMP-specific phosphodiesterases: tissue distribution, drug sensitivity, and regulation of cyclic GMP levels, Advances in Second Messenger and Phosphoprotein Research (Raven Press, New York) p. 271.

Aono, J., M. Akima and K. Sakai, 1981, Effects of *N*-(2-hydroxyethyl) nicotinamide nitrate (SG-75) on methacholine-induced ECG changes in intact anesthetized rats, Jpn. J. Pharmacol. 31, 823.

Beavo, J.A. and D.H. Reifsnyder, 1990, Primary sequence of cyclic nucleotide phosphodiesterase isozymes and the design of selective inhibitors, Trends Pharmacol. Sci. 11, 150.

Corliss, R.J., D.H. McKenna, S. Sialer, G.S. O'Brien and G.G. Rowe, 1968, Systemic and coronary hemodynamic effects of vasopressin, Am. J. Med. Sci. 256, 293.

Dundore, R.L., P.F. Pratt, W.D. Hallenbeck, M.L. Wassey, P.J. Silver and R.A. Buchholz, 1990, Sodium nitroprusside potentiates the depressor response to the phosphodiesterase inhibitor zaprinast in rats, Eur. J. Pharmacol. 185, 91.

Dundore, R.L., P.G. Habeeb, P.F. Pratt, L.T. Becker, D.M. Clas and R.A. Buchholz, 1992, Differential hemodynamic responses to selective inhibitors of cyclic nucleotide phosphodiesterases in conscious rats, J. Cardiovasc. Pharmacol. 19, 937.

Hall, I.P., 1993, Isoenzyme selective phosphodiesterase inhibitors: potential clinical uses, Br. J. Clin. Pharmacol. 35, 1.

Holzmann, S., 1983, Cyclic GMP as possible mediator of coronary arterial relaxation by nicorandil (SG-75), J. Cardiovasc. Pharmacol. 5, 364.

Ignarro, L.J., H. Lippton, J.C. Edwards, W.H. Baricos, A.L. Hyman, P.J. Kadowitz and C.A. Gruetter, 1981, Mechanism of vascular smooth muscle relaxation by organic nitrates, nitrites, nitroprusside and nitric oxide: evidence for the involvement of *S*-nitrosothiols as active intermediates, J. Pharmacol. Exp. Ther. 218, 739.

Isono, T., Y. Koibuchi, N. Sato, A. Furuichi, M. Nishii, T. Yamamoto, J. Mori, M. Kohsaka and M. Ohtsuka, 1993a, Vasorelaxant mechanism of the new vasodilator, FK409, Eur. J. Pharmacol. 246, 205.

Isono, T., N. Sato, Y. Koibuchi, S. Sakai, T. Yamamoto, R. Ozaki, J. Mori, M. Kohsaka and M. Ohtsuka, 1993b, Effect of FK409, a novel nitric oxide donor, on acute experimental myocardial ischemia, Jpn. J. Pharmacol. 62, 315.

Kodama, K., H. Adachi, T. Ogawa and H. Ohhara, 1992, Inhibitory effect of a novel antianginal agent, E4080, on ST segment elevation induced by vasopressin in anesthetized guinea pigs, Jpn. J. Pharmacol. 60, 73.

Leier, C.V., 1985, Nitrate tolerance, Am. Heart J. 110, 224.

Matlib, M.A., G.P. Dube, R.W. Millard, D.A. Lathrop, Y.H. Baik, K. Sakai, J. DiSalvo and A. Schwartz, 1985, Studies on the mode of action of isosorbide dinitrate: a physiologic and biochemical approach, Am. Heart J. 110, 204.

Murray, K.J., 1993, Phosphodiesterase VA inhibitors, Drug News Perspectives 6, 150.

Popescu, L.M., C. Panoiu, M. Hinescue and D. Nutu, 1985, The mechanism of cGMP-induced relaxation in vascular smooth muscle, Eur. J. Pharmacol. 107, 393.

Raeymaekers, L., F. Hofmann and R. Casteels, 1988, Cyclic GMP-dependent protein kinase phosphorylates phospholamban in isolated sarcoplasmic reticulum from cardiac and smooth muscle, Biochem. J. 252, 269

Saeki, T., H. Adachi and I. Saito, 1993, A novel selective and potent inhibitor of cGMP-phosphodiesterase, E4021, as an anti-anginal drug, in vitro, Circulation 88, I-38.

Schoeffter, P., C. Lugnier, F. Demesy-Waeldele and J.C. Stoclet, 1987, Role of cyclic AMP- and cyclic GMP- phosphodiesterases

in the control of cyclic nucleotide levels and smooth muscle tone in rat isolated aorta, Biochem. Pharmacol. 36, 3965.

Silber, S., 1990, Nitrates: why and how should they be used today?, Eur. J. Clin. Pharmacol. 38 (Suppl. I), S 35.

Souness, J.E., R. Brazdil, B.K. Diocee and R. Jordan, 1989, Role of selective cyclic GMP phosphodiesterase inhibition in the myorelaxant actions of M&B 22,948, MY-5445, vinpocetine and 1-methyl-3-isobutyl-8-(methylamino) xanthine, Br. J. Pharmacol. 98, 725.

Szilvassy, Z., I. Jakab, P. Ferdinandy, M. Koltai, J. Lonovics, T. Tarrade and P.G. Braquet, 1993, Zaprinast, cicletanine, and verapamil attenuate overdrive pacing-induced myocardial ischemia in conscious rabbits, Life Sci. 53, 13.

Twort, C.H.C. and C. Van Breemen, 1988. Cyclic guanosine monophosphate-enhanced sequestration of Ca^{2+} by sarcoplasmic reticulum in vascular smooth muscle, Circ. Res. 62, 961.

Weishaar, R.E., D. Kobylarz-Singer, J.A. Keiser, C.D. Wright, J. Cornicelli and R. Panek, 1992, Cyclic nucleotide phosphodiesterases in the circulatory system: biochemical, pharmacological, and functional characteristics, Advances in Second Messenger and Phosphoprotein Research (Raven Press, New York), p. 249.

Yamada, H., F. Yoneyama, K. Sato and N. Taira, 1991, Cardiohemodynamic effect of FK409, a novel highly potent nitrovasodilator, in anesthetized dogs, Eur. J. Pharmacol. 205, 81.